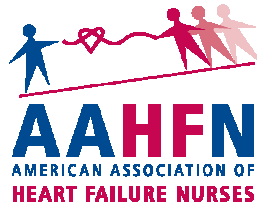


Selected Topics on Genetics for Nurses Specializing in Heart Failure



Theresa A. Beery PhD, RN, ACNP
Professor
University of Cincinnati College of Nursing
Cincinnati, OH

Objectives:

1. Describe three ways that genetics/genomics can affect care of the heart failure patients.
2. Explain the use of pharmacogenetics to better tailor warfarin dosing to individual patients.
3. Apply knowledge about direct-to-consumer genetic testing to hypothetical patient care situations.
4. List three web-based resources for up-to-date genetic information.

Introduction:

While genetics/genomics has many applications for nurses engaged in the care of patients with heart failure, for many updating genetics knowledge is buried beneath more immediate concerns about maintaining a patient's hemodynamic stability and medication management. Genetics is relevant to everyday practice now and the ways in which genetics affects how we care for our patients are increasing. This CE offering will address pharmacogenetics for heart failure practice, genetic testing, and staying current in genetic applications. Overviews designed to help practicing nurses update their genetics literacy are available (1). Since the completion of the Human Genome Project in 2003, the lay press has been filled with information about the importance of genetics to everyday life and our patients are asking important questions about their genetic health (2,3). We are even starting to see the application of genetics to diet choices for patients and others in the growing field of Nutrigenomics (4,5).

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Advances in Genetics Relevant to Heart Failure:

Heart failure is a complex disease and multiple physiological pathways have been implicated in its generation. These include variations in energy production and regulation, variations in calcium processing and problems in signaling the initiation of DNA transcription (6). Genomics has been used to improve our understanding of the origins of cardiomyopathies (7). Investigations have identified genetic factors that increase heart failure risk including ACE gene polymorphisms that are associated with vascular stiffness and polymorphism in sympathetic neuroreceptors (6). Potential therapeutic targets, such as the cardiac ryanodine receptor, have been identified (8). The American Heart Association Scientific Statement on the Prevention of Heart Failure has identified “obtaining a much better knowledge of genetics and HF,” as an important focus for future research (6).

Pharmacogenetics:

Pharmacogenetics offers the promise of providing a more individualized dosing of medications which will reduce or even eliminate life-threatening adverse reactions (9). Pharmacogenetics may seem like a new term but it was actually first used in 1959 to describe variations in individual responses to isoniazid administration (10). In 2007 the FDA described pharmacogenomics in this way:

The action of drugs in the human body is influenced by an individual's genetic background: however, this background is unique for each individual. Therefore, two individuals can react quite differently to the same drug. Pharmacogenomics is the field exploring these differences, providing new knowledge and tools to treat people on an individual basis. Often, the result of this research is referred to as "personalized" or "targeted medicine”

(11).

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Genetic variations in proteins involved in metabolism, as drug transporters, or drug targets will affect how people respond to the medications used to treat them. The testing that is most commonly available evaluates effectiveness of liver enzymes in the cytochrome P-450 (CYP-450) system. Persons tested can be classified as poor, extensive or ultra-rapid metabolizers based on common genetic variations not currently associated with disease. When an active drug is given, poor metabolizers will have more difficulty clearing that drug and will have higher than normal blood levels for longer periods at standard doses. They will be more likely to develop adverse reactions and dose limiting toxicities. Persons who are ultra-rapid metabolizers will clear the drug quickly and may have no therapeutic effect. When a pro-drug is given (such as codeine which must undergo biotransformation to morphine to have clinical effect) the response is just the opposite. Poor metabolizers will have little therapeutic effect because they are unable to effectively metabolize codeine to morphine. The ultra-rapid metabolizers will convert codeine efficiently and be more prone to adverse reactions (9,12).

There have been successes and more marginal results in the relatively young field of pharmacogenetics. Pharmacogenetic testing for use of the drug Herceptin in breast cancer treatment has been an unequivocal success. The drug works well to treat HER2-overexpressing breast cancers, which account for approximately 25% of breast cancers and is often more aggressive. When tumor cells are tested, the results will determine whether or not Herceptin is an appropriate treatment (13,14).

Pharmacogenetic testing is also available for prescribing psychotropic drugs such as the serotonin reuptake inhibitors (SSRI) commonly used to treat depression. Despite what many thought were promising results, recent evaluation of available evidence indicated that there are insufficient data to support the clinical utility of pharmacogenetics testing to determine appropriate selection and dosing of SSRI's for treatment of non-psychotic depression (15).

Safe warfarin dosing is of great interest to anyone caring for persons with

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cardiovascular disease. There has been significant progress in our understanding of genetic variations in how people use warfarin physiologically and much of that information is now available for clinical practice. Warfarin is metabolized by the liver enzyme *CYP2C9*, which is one of the CYP-450 enzymes. Persons who have polymorphisms (common variations in DNA sequence) in this gene have an increased risk of above range INR. They also take longer to stabilize warfarin dose, have episodes of bleeding earlier during the time of warfarin therapy, and have more serious events of over-coagulation or life-threatening bleeding (16).

Warfarin works by inhibition of Vitamin K epoxide reductase (*VKORC1*). There are common variations in the DNA sequence of the gene coding for this protein that alter warfarin dose requirements (17). Studies have supported the need to lower warfarin doses in persons who have genetic variations in *VKORC1* (18). Based on mounting evidence, the FDA recently approved a change in the label of warfarin to include information related to pharmacogenetics testing. The package insert currently reads, “lower initiation doses should be considered for patients with certain genetic variations in *CYP2C9* and *VKORC1* enzymes” (19). A website now provides an algorithm to assist with selecting appropriate dosing for patients taking warfarin (<http://www.warfarindosing.org/Source/Home.aspx>).

In addition to *CYP2C9* and *VKORC1* results, the website has space to input a variety of lifestyle (e.g. smoker) and clinical information (e.g. liver disease). It is supported by the National Institutes of Health, the Barnes-Jewish Hospital Foundation, the American Heart Association, and a commercial sponsor (20). Of course, even with the best and most comprehensive assessment for genetic and environmental predictors of response, INR monitoring still remains the gold standard.(20). It has been estimated that a patient’s genotype for *CYP2C9* and *VKORC1* combined with age, sex and weight only account for approximately 45-60% of the variation in response to warfarin dose (21).

Genetic testing for warfarin dosing can be purchased at prices ranging from about \$175.00 - \$550.00. Time from submission of sample to receipt of results varies. Major

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medical centers can provide results to their on-site clients in one day or less, while internet based companies promise results in three-eight days (22,23). CPT codes are now available for genetic testing for warfarin response. Harvard Medical School offers warfarin response testing with a 36-48 hours turnaround and lists CPT codes for billing as do many other laboratories with long histories of genetic testing for heritable diseases such as Cincinnati Children's Hospital Medical Center (24). The Genetic Pharmacology Service at CCHMC has an abundance of resources for patients, families, and healthcare professionals about pharmacogenetics testing (also called dose response testing) in general, specific tests, and how to order tests (25).

Direct-to-Consumer Genetic Testing:

Clinical genetic testing is available from a variety of sources for over 1200 genetic diseases with a very fragmented effort at oversight (26,27). Over the years genetic testing has been ordered by genetics professionals in conjunction with genetic counseling. Now many genetic tests are available over the counter or, more accurately, over the internet from a growing number of vendors with no healthcare professional serving as an intermediary (26,27). Some companies offer support from genetic counselors before testing, some offer support after testing and some do not have genetic counselors on staff (28).

Multiple companies are marketing genetic testing direct-to-consumers, often providing confusing results with minimal, if any, counseling support (26). Tests offered include dose response testing (pharmacogenetics), diagnostic or predictive testing for genetic diseases, ancestry and paternity testing. Some of these companies include or require consultation with a genetic counselor and others do not. This raises a major concern about how consumers will understand and their results and if major life decisions will be based on poorly understood genetic tests (28-30).

In an effort to take a stand on this controversial issue, the American Society of Human Genetics has issued a statement on direct-to-consumer (DTC) genetic testing addressing concerns related to the context and quality of testing, unsubstantiated claims, and

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the need for consumers to make informed choices (26). They note that companies are often making claims that are either exaggerated or unsubstantiated by scientific evidence and that this can lead to consumers have inaccurate expectations regarding the meaning of their results. Furthermore, many of the companies doing DTC testing do not disclose the sensitivity and specificity of the tests they are using (26,27).

Three companies offering genome-wide scans are the latest additions to the world of internet-based direct-to-consumer genetic test. These companies will scan genome results looking for sequence variations that have been associated with disease according to the current literature. The cost is around \$1,000.00. The reports provided are somewhat varied, but they typically include risk in percentage of traits as varied as tasting bitterness in broccoli to having cardiovascular disease (31,32). One concern is that while the scans may be based on current literature, the literature on genetic association is dynamic; an area of the genome that may appear important in increasing risk today may turn out to be much less important tomorrow.

Staying Current in Genetics:

Staying current in genetics is always a challenge with the literature growing constantly. Textbooks are frequently outdated before they go to press. Web-based resources are crucial sources of up-to-date genetic information, but the concern about accuracy is always present. Some internet-based resources provide animated tutorials to review of basic genetic principles.

Included is a listing of some reliable, current, and accessible web-sites for expanding and maintaining genetic literacy (see table 1. A highly recommend site is <http://www.genetests.org> *Gene Reviews* for up-to-date expert authored and peer-reviewed information on genetic disease. Genetic literacy is essential for every practicing nurse and genetic applications to bedside care will undoubtedly continue increasing.

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Web-based Resources for Staying Current in Genetics:

Dolan Learning Center: <http://www.dnalc.org/home.html>

Provided by Cold Spring Harbor Laboratory, the Dolan Learning Center offers a variety of resources in support of genetics education.

Genetics and Your Practice: <http://www.marchofdimes.com/gyponline/index.bm2>

Sponsored by the March of Dimes this web-site provides information about genetic testing, collecting family and social history and genetics referrals.

Genetics Home Reference <http://ghr.nlm.nih.gov/>

From the National Library of Medicine this site provides a wealth of information for both clinicians and consumers.

Gene.tests.org: <http://www.genetests.org>

Funded by the NIH and maintained by the University of Washington, this web site provides reviews of genetic diseases and locations of clinical and research genetic testing. Provides an excellent on-line genetics glossary.

National Human Genome Research Institute (NHGRI): <http://www.genome.gov>

Many resources for educational support; this site includes information on health policy and legal ethical issues related to genetics.

The Online Mendelian Inheritance in Man: <http://www.ncbi.nlm.nih.gov/omim/>

Is a catalog of human genes and genetic disorders developed by Dr. Victor A. McKusick and Johns Hopkins University. It provides textual and reference information, and links to the PubMed database and gene sequence information.

The University of Utah, Genetic Science Learning Center: <http://gslc.genetics.utah.edu/>

The GSLC offers a very clear resource for basic genetics information including animations.